Support for the amendments can be found throughout the specifications including the parent applications Serial No. 08/261,388, now abandoned and Serial No. 08/477,809, now U.S. Patent No. 5,807,522. The recitations of "essentially free of cross-contamination" and "individually applied" DNA sequences in amended claims 7 and 34 find support in the specifications describing methods of forming microarrays by separately depositing reagents at different positions on the microarray. Specifically, the limitation is disclosed in the instant application on page 11, line 26 through page 12, line 12, as well as in Serial No. 08/261,388, now abandoned on page 12, lines 14 -29 and Serial No. 08/477,809, now U.S. Patent No. 5,807,522 on page 17, lines 17-28.

An issue of new matter is not raised by these amendments. Entry thereof is respectfully requested. Upon entry of this Amendment, claims 7 through 40 are now pending.

(b) Informalities:

Objection to the drawings previously indicated by the Examiner is acknowledged. Corrected drawings are submitted concurrently to box draftsman.

Notification to comply with the requirements directed to applications containing nucleotide and/or amino acid sequences is also acknowledged. Submitted herewith are amendments to the specification which include SEQ ID NOS to accompany the sequences at page 41 of the instant application. Thus, the sequence disclosures are in compliance with 37 CFR §§ 1.821 through 1.825.

(c) Interview Summary

Applicants' attorney and agent greatly appreciate the courtesy that was extended by the Examiner. During the interview on March 7, 2002, the parties discussed about the new matter and art rejections raised in the Final Office Action dated December 18, 2001. The Examiner requested that the Applicants provide a summary of the interview.

During the interview the Examiner agreed to withdraw the new matter rejections concerning the numerical limitation "400 or more discrete regions" and the density requirement of "62,500 regions/cm^2" for the following reasons.

The priority specifications generally describe a high density array with 400 or more discrete regions. For instance, the second priority application filed June 7, 1995 depicts and describes two exemplary high density arrays of different sizes. Each of these arrays has more than 400 discrete regions and has a density of about 400 or more discrete regions per cm^2 (see Figures 5-6 and description at page 10, first paragraph). The specific examples provided in the priority documents are not meant to limit the scope of the teaching, but rather to provide illustrative examples to facilitate one skilled in the art to follow the disclosed teachings.

Int. Sum. approved
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Similarly, the density requirement of "between about 62,500 regions/cm^2 and about 625 regions/cm^2 also finds support in the priority specifications. The density range flows directly from the disclosure in all the applications that the region diameters are between about 20 and 200 μm, and the distance between the regions in the microarray preferably should be separated from one another by about the same distance as the diameter of the regions (see first priority specification at page 13 lines 9-16). During the interview, the Examiner recalculated the conversion and confirmed the accuracy of Applicants' claimed range of density.

With respect to the lack of contamination recited in claims 7 and 34, Applicants hereby amend those claims to clarify what is claimed therein. Specifically, claim 7 has been amended to recite "each region in the microarray is essentially free of cross contamination with DNA sequences individually applied to the other regions in the microarray." Similarly, claim 34 has been amended to recite that the regions are "essentially free of cross-contamination by individually applied DNA sequences unique to others of said 400 regions."

These amended claims more particularly point out and describe the lack of cross-contamination, while disclosing that it is achieved in a particular way. This limitation finds support in, among other places, priority application Serial Nos. 08/261, 388 (great-great grandparent) and U.S. Patent No. 5,807,522 (great-grandparent). For example, the great-great grandparent application recites on page 12:

> "After depositing a bead at one selected location on a support, the tip is typically moved to a corresponding position on a second support, a droplet is deposited at that position, and this process is repeated until a liquid droplet of the reagent has been deposited at a selected position on each of a plurality of supports.
>
> The tip is then washed to remove the reagent liquid, filled with another reagent and this reagent is now deposited at each another array position on each of the supports. In one embodiment, the tip is washed and refilled by the steps of (i) dipping the capillary channel of the device in a wash solution, (ii) removing wash solution drawn into the capillary channel, and (iii) dipping the capillary channel into the new reagent solution."

The great-great grandparent application also describes the individual deposition of "known" amounts, "selected" solutions at "selected" regions, and the formation of a "desired" microarray on page 16 line 8, page 6 line 6, and page 13 lines 18, respectively. Inherent in these disclosures is the individual deposition of DNA samples that precludes cross contamination by the unintended deposition of unknown reagents. This disclosure also provides support for step (b) in claim 21, which was requested by the Examiner in his Office Action dated December 18, 2001.

To the extent that both limitations find support in the priority specifications, they do not constitute new matter. Thus, the claims as amended are entitled to the earliest priority date of the great-great grandparent application of June 17, 1994.

(d) Rejections under § 102(e) and 35 U.S.C. § 103:

The Office Action cites U.S. Patent Nos. 6,013,440 (by Lipshutz et al.) and 5,723,320 (by Dehlinger) against all pending claims. As discussed in Applicant's Response the Office Action dated March 3, 2001, the Lipshutz patent application was filed on March 10, 1997 claiming priority to a provisional application dated March 11, 1996. Thus, the earliest possible priority date of this reference is March 11, 1996. The Dehlinger patent application was filed on August 29, 1995, more than a year after the filing of Applicants' earliest priority specification.

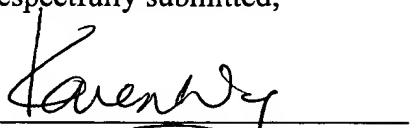
In light of these priority dates, U.S. Patent Nos. 6,013,440 (by Lipshutz et al.) and 5,723,320 (by Dehlinger) neither anticipate the claimed subject matter nor render the subject matter obvious. To the extent that the objected terms and hence the rejected claims as a whole are entitled to the priority date predating the filing of the two cites references, the rejections under 35 U.S.C. § 102(e) and 35 U.S.C. § 103(a) are improper. Withdrawal of these rejections is respectfully requested.

III. CONCLUSION

Applicants respectfully submit that the above amendments and remarks fully respond to the rejection made in the Final Office Action mailed December 18, 2001. Applicants submit that the claims as amended are in allowable form and condition.

If the Examiner believes a telephone interview would further prosecution of this case, the Examiner is invited to call the undersigned at (650) 463-8100.

Respectfully submitted,



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Version with Markings to Show Changes Made

In the Specification:

The paragraph beginning from line 29 at page 41 has been replaced with the following

Plasmid DNA was isolated and inserts from each clone were amplified by use of the polymerase chain reaction (PCA) and purified. Inserts were amplified by PCR in a 96-well format using primers (PN132, 5'CCTCTATACTTTAACGTCAAGG (SEQ ID NO.1); PAN133, 5'TTGTGTGGAATTGTGAGCGG (SEQ ID NO.2)) complementary to the 1YES polylinker and containing a six carbon amino modification (Glen Research) on the 5' end. PCR products were purified in a 96-well format using QIAquick columns (Qiagen).

In the Claims:

Claims 7, 21 and 34 have been amended as follows:

7. (Amended) A substrate with a surface comprising a microarray of DNA sequences, wherein (i) the microarray has a density of about 400 or more discrete regions of DNA sequences per cm^2 of substrate surface, (ii) the DNA sequences are isolated polynucleotides, (iii) the microarray comprises 400 or more regions, and (iv) the DNA sequences contained in each discrete region are at least about 50 subunits in length, each region in the microarray is essentially free of cross-contamination with DNA sequences individually applied to the other regions in the microarray.

21. (Amended) A substrate with a surface comprising a microarray of DNA sequences, wherein the DNA sequences are polynucleotides, produced by a method comprising the steps of

(c) depositing a selected volume between about 0.002 nl and about 2 nl of a solution comprising a selected, isolated polynucleotide at a discrete region on the surface of the substrate, and

(d) repeating step (a) at other locations on the surface of the substrate until a microarray of 400 or more regions is formed, wherein the regions are at a density of at least about 400 regions/cm^2 ~~between about 62,500 regions/cm^2 and about 625 regions/cm^2~~.

34. (Amended) A substrate with a surface comprising a microarray of DNA sequences and suitable for analysis of a polynucleotide mixture, wherein (i) the microarray has a density of about 400 or more discrete regions of DNA sequences per cm^2 of substrate surface; (ii) each of said regions contains, as an isolated polynucleotide, a unique DNA sequence having at least about 50 subunits; (iii) the microarray comprises at least 400 regions essentially free of cross-contamination by individually applied DNA sequences unique to others of said 400 regions, such

that the DNA sequences in said regions are selective in hybridizing with corresponding members of said mixture.

The following new claim 40 has been added:

40. (New) The substrate of claim 21, wherein the regions are at a density between about 62,500 regions/cm^2 and about 625 regions/cm^2.